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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,784	05/26/2000	Christopher L. Baszczynski	5718-23B	9894

29122 7590 09/23/2003

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	21

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.	Applicant(s)
09/579,784	Baszczynski et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 28, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10, 13-24, and 27-29* is/are rejected.

7) ☒ Claim(s) *11, 12, 25, and 26* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *18*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed July 28, 2003, Paper No. 20.

Claims 1-29 are pending in the instant application.

Any rejections not repeated in this Office action are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Maintained Rejections

Claims 1-10, 13-24, 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record set forth in the previous Office action mailed March 16, 2003, Paper No. 17.

Applicant's arguments filed July 28, 2003 have been fully considered but they are not persuasive. Applicants argue that one of skill in the art would clearly understand the claimed invention, that the homologous structures of the RNA blocks would have the same sequences as the target gene, with an interposed (DNA block) heterologous sequence. Contrary to Applicants assertions, the invention that is claimed is not clearly described in the claims, and not clearly comprehendible to one skilled in the art. The specification and figures provide accompanying guidelines for understanding the scope and utilization of the claimed invention, but the claims themselves must set forth more clearly what is being claimed. The metes and bounds of what is

being claimed is not set forth in the language of the claims. There is a generic description of a chimeric oligonucleotide recited in the claims, but the duplex structure provided by the complementarity of the oligonucleotide residues in the blocks of nucleotides cannot be discerned from the language of the claims (e.g. Is the duplex a function of terminal complementary sequences that form a hairpin for stability and flank the major portion of the chimeric structure, or is the duplex the major structure of the chimeric oligonucleotide, brought about by the complementarity of longer stretches of DNA/RNA sequences that function as a duplex in introducing the mutation into a target nucleic acid? Is the DNA containing the mismatch part of the duplex structure?). In addition, there is no indication of the limitations of the lengths of nucleotide sequences of the RNA or DNA blocks (Is it 2 nucleotides? Five? 1,500 nucleotides? Are the homologous sequences, together, contiguous with the sequences of the target gene? Or interspersed? Is the DNA mismatch contiguous with the flanking sequences, relative to the target gene?) Appropriate clarification is requested.

Claims 1-10, 13-24, 27-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the previous Office action mailed March 16, 2003, Paper No. 17.

Applicants argue that sufficient written description has been provided by the claim language and by the teachings in the instant disclosure to immediately discern the limitations at

issue in the claims. Contrary to Applicants' assertions, the claimed invention reads very broadly on chimeric oligonucleotides comprising 2 blocks of RNA residues that are homologous to any herbicide resistance gene, and of any length, and which contain an intervening DNA sequence of any length which comprises a nucleotide mismatch that confers herbicide resistance to a plant. It is unclear what comprises the genus of single nucleotide mismatches that confer herbicide resistance to a plant. It is also unclear what the genus encompasses that comprises the RNA blocks that flank the DNA block (e.g. This broad genus reads on as few as two RNA nucleotides flanking a single DNA residue, or 1500 RNA residues flanking a single DNA residue, and which 1500 RNA residues are homologous to different herbicide resistant genes, or homologous to different regions of the herbicide resistant gene, or have overlapping sequences that are homologous to an herbicide resistant gene, or any permutation imaginable.)

Applicants argue that ample structure and function is shared among members of the claimed invention to demonstrate possession of the claimed generic chimeric oligonucleotide structures. Contrary to Applicants' assertions, the claims do not adequately describe the chimeric oligonucleotide structures that they intend to embrace. The lengths of the flanking RNA sequences are highly variable, their spatial relationship to each other, relative to their homology with a target herbicide resistant gene, is also highly variable (e.g. Do each of the flanking sequences target separate regions of the same target gene? Are they contiguous to each other regarding the homologous target gene sequence? Do they contain intervening DNA sequences of

long stretches, short stretches, intermediate stretches of a different target gene? None of this is clearly described in the claims.).

Applicants argue the claimed invention is adequately described because a common spatial relationship is shared between the claimed RNA and DNA blocks. Contrary to Applicants' assertions, the common spatial relationship shared between the RNA and DNA blocks, that the DNA is intervening, does not suffice in providing adequate written description for the broadly claimed invention. While it can be discerned that the DNA intervenes between the RNA blocks, it is unclear how many residues exist within each block, whether the homologous sequences of RNA are contiguous with corresponding homologous target sequences, or whether the intervening mismatched DNA block is also contiguous with the flanking homologous RNA sequences in relation with the target gene sequence.

Applicants argue that adequate written description is provided because the chimeric oligonucleotide of claims 1 and 16 share a common structure within the RNA blocks. Contrary to Applicants' assertions, the description provided, that the RNA blocks are homologous to target gene sequence, does not adequately describe the invention. It is unclear how many nucleotides, or the range of nucleotide lengths, are comprised within these RNA blocks, and whether the homologous sequences of the two blocks are contiguous with each other, and with the interceding DNA block. The claimed invention includes RNA blocks that target two, spatially distinct nucleotide sequences of the target gene sequence, as well as contiguous sequence stretches. The claims embrace blocks as small as a single nucleotide, and as large as thousands of nucleotides.

Applicants argue that adequate written description is provided because the chimeric oligonucleotide of claims 1 and 16 comprise a common structure of a block of DNA residues, which comprise a modifying sequence of DNA for generating at least one mismatch to the target sequence. Contrary to Applicants' assertions, it is unclear whether the DNA block which is intended to introduce at least one mismatch into the target gene comprises sequences that are contiguous with the flanking RNA blocks, whereby the homologous sequences of the three blocks (with the exception of the nucleotide mismatch) are contiguous with the intended target gene sequence, or non-contiguous. The claims encompass non-contiguous blocks of nucleotides that target different portions of a target gene sequence, as well as contiguous ones.

Claims 1-8, 13-22, 27-29 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the previous Office actions mailed April 9, 2002 and March 16, 2003, Paper Nos. 9 and 17, respectively.

Applicant's arguments filed July 28, 2003 have been fully considered but they are not persuasive. Applicants argue that the full scope of the invention is enabled, which is drawn to the inactivation of any nucleotide sequence of interest introduced into a genome of any plant cell comprising the transformation of the plant cell with a chimeric oligonucleotide comprising two RNA blocks of nucleotides (of any length) that are homologous to (any regions of) the introduced target gene sequence, which RNA blocks flank a block of DNA (of any length) comprising at least one nucleotide mismatch to the target nucleotide sequence. Contrary to Applicants' assertions, the examples provided of the targeting and nucleotide conversion of

AHAS in maize plant cells, and of the targeting and nucleotide conversion of previously transformed GFP, using chimeric oligonucleotides illustrated in figures 1-13, are not representative of the ability to inactivate any nucleotide sequence of interest introduce into the genome of a plant. The chimeric oligonucleotides successfully employed comprised nucleotide sequences ranging from 60-100 nucleotides, and introduced single point mutations into the previously characterized genes, including AHAS, which had previously identified mutagenesis data (identifying a single point mutation) that converted AHAS from a herbicide susceptible to a resistant gene. It would require undue experimentation beyond that reported in the art, and beyond that disclosed in the instant specification, to determine the desired single point mutations converting any and/or all target genes from active to inactive forms.

Applicants argue that the method of introducing a nucleotide conversion using the instantly claimed chimeric oligonucleotides is a predictable endeavor and therefore the full scope of the claimed invention is enabled. Contrary to Applicants' assertions, the specification teaches (e.g. table 2 on page 26; text on pages 27-31) that nucleotide conversions do not consistently reflect the mismatches anticipated by the DNA block sequences containing the nucleotide mismatch within the chimeric oligonucleotides (see for example page 29, line 24-page 30, line 13). Therefore, the claimed method for the inactivation of any target gene introduced into any plant genome comprising the administration of chimeric oligonucleotides comprising two RNA blocks of any length, flanking a DNA block of any comprising at least one nucleotide mismatch of the target gene sequence, was highly unpredictable at the time the invention was made.

Applicants argue that the examples provided in the instant specification, including the specific guidance for target sites in EPSPS or ALAS, and the additional references that identify single point mutations within the ALS target gene that convert it to a herbicide resistant form from a herbicide susceptible form in tobacco, are enabling for the full scope claimed. Applicants' assertions are correct in part, in that the higher order genomic structure of tobacco plant cells does not render target gene nucleotide changes unpredictable using the chimeric oligonucleotide particularly described by Kochevenko et al. However, it would require undue experimentation beyond that known in the art to predictably inactivate any target gene of interest introduced into any host plant genome by administering chimeric oligonucleotides of any length and comprising at least one nucleotide mismatch. The target genes previously taught in the art (e.g. ALS, GFP) or in the instant disclosure (EPSPS or AHAS) have been extensively characterized and single point mutations of particular amino acid residues have been identified within these target genes, which, when obtained, convert them from herbicide sensitive to herbicide resistant genes. It would require undue experimentation beyond that taught previously or in the instant disclosure to identify nucleotide mismatches in any and/or all target genes of interest (including any and/or all herbicide resistant genes) that would convert these target genes from active to inactive forms. This, combined with the unpredictability illustrated in the instant disclosure of inserting anticipated nucleotide mismatches into the target genes using chimeric oligonucleotides comprising DNA blocks with the anticipated nucleotide mismatch, render the claimed method highly unpredictable.

Allowable Subject Matter

Claims 11, 12, 25, 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703)

305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

September 15, 2003